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This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1740076> since 2020-07-07T10:59:20Z

Published version:

DOI:10.1016/j.cortex.2020.04.027

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(Article begins on next page)

Title: Following the gold trail: reward influences on spatial exploration in neglect

Running title: Reward influence on hemispatial neglect

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ABSTRACT

Spatial attention is guided by the perceived salience and relevance of objects in the environment, a process considered to depend on a broad parieto-frontal cortical network. Signals arising from the limbic and nigrostriatal pathways conveying affective and motivational cues are also known to modulate visual selection, but the nature of this contribution and its relation to spatial attention remain unclear. We investigated the role of reward information in 15 patients with left hemispatial neglect and 15 control subjects playing multiple rounds of a virtual foraging game. Participants' exploration tracked dynamically adjusted underlying reward distributions, largely unbeknownst to them. Both control and neglect participants showed typical exploration/exploitation balance dependent on abundance or scarcity of rewards. De-reinforcing previously favored, mostly right, regions of space attenuated left space under-exploration in patients. Multiple regression analysis indicates that such reward-based training may benefit mostly patients early after lesion onset, with mild neglect and small lesions sparing subcortical regions. Our findings support the view that spatial exploration recruits heavily right hemispheric visuospatial attentional mechanisms as well as reward signals processed by basal ganglia and prefrontal cortical circuits, which serve to learn about the motivational relevance of environmental stimuli and help prioritize attention and motor response selection.

Keywords: neglect, reward, foraging, cortex, basal ganglia

1. INTRODUCTION

Selective attention is a main gateway for higher-order sensory information processing. It is common to distinguish between stimulus-driven attention, causing us to orient automatically toward salient events and voluntary attention, which selects particular objects or spatial locations according to current goals and intentions. In addition to these well-studied processes, there is growing evidence that attention is influenced by learned reward associations (Hickey *et al.*, 2014; Chelazzi *et al.*, 2014). This is not surprising, as the brain has evolved to learn about stimuli that signal reward opportunities. Foraging animals decide to occupy patches where food is abundant and disengage from depleted ones using time-varying reward signals and they learn about reward-predictive features of their environment in the process (Stephens, 2008). Studies have begun to explore how reward history competes with stimulus-driven and goal-directed attention and have shown, for example, that previously rewarded but task-irrelevant visual items can capture attention and interfere with performances during cued-detection (Munneke *et al.*, 2015) or search tasks (Bourgeois *et al.*, 2016).

Cerebral damage can lead to impairment in spatial orienting, as illustrated by the neurological syndrome of unilateral spatial neglect (Bisiach and Vallar, 2000; Heilman *et al.*, 1993). The deficit observed in patients with neglect offers an opportunity to investigate possible interactions between reward and attention mechanisms at the brain level. Neglect arises from lesions within a broad fronto-parietal network (Corbetta and Shulman, 2011) and is characterized by a failure to report or act upon stimuli presented in contralesional space - typically the left side as a result of a right hemispheric lesion - despite intact early sensory processing (Driver and Vuilleumier, 2001). Such deficits bear upon both stimulus-driven and goal-directed attention (Corbetta and Shulman, 2002; Bays *et al.*, 2010). Interestingly, neglect is also modulated by the emotional and motivational contents of stimuli. For instance, patients with left neglect fail to report a neutral stimulus displayed in the contralesional field when simultaneously presented with an ipsilesional one, but detection improves when left stimuli are emotionally-loaded images of frightful faces, gory scenes or spiders (Vuilleumier and Schwartz, 2001a; Vuilleumier and Schwartz, 2001b; Grabowska *et al.*, 2011; Tamietto *et al.*, 2007). This suggests that emotional cues undergo independent processing in intact brain structures and can somehow boost neural activity in the attention orienting network (Domínguez-Borràs *et al.*, 2012). An early report showed that detection performance of a patient with left neglect was improved by rewarding each detected target with one penny (Mesulam, 1985). In a similar vein, patients showed better performance on a paper and pencil item cancellation test when the items were images of £1.00 coins and the experimenter

promised a monetary reward for each cancelled target, than when the items were images of brass buttons and there were no reward instructions (Malhotra *et al.*, 2013). Although such results could merely reflect non-specific effects on motivation or arousal level, other investigators have attempted to selectively enhance the motivational value of left-sided stimuli in the context of visual search performance (Lucas *et al.*, 2013) or forced-choice between two lateralized targets (Lecce *et al.*, 2015). Their results indicate that neglect patients show reduced rightward attentional bias when the highest reward probability was associated with left spatial locations, thus suggesting a role of the cortical-striatal circuits linked to the dopaminergic reward system in mediating such effects.

These results suggest that when performing an attention task, reward information is processed by non-damaged structures that could indirectly and independently supply modulatory inputs into a hypothetical saliency map. Although reward-based manipulations can counteract the consequences of core attentional and awareness impairments in patients, several aspects need to be explored in more detail: whether neglect patients and normal subjects show qualitatively similar ability to learn about rewards during spatial exploration, whether similar principles govern immediate, short-range processing of reward signals and more long-term learning about reward distributions, whether reward effects take place above or below the radar of conscious awareness and whether the observed changes are context-specific or generalize to other spatial tasks. Addressing such questions could help better understanding of the neurocognitive mechanisms by which reward information guides spatial exploration.

Here, we address these questions in the context of virtual foraging for hidden rewards. We asked whether patients with neglect respond to reward distributions during spatial exploration and learn to orient to high-value stimuli located in the attentional shadow of the neglected field. We used a foraging task modelled on classical paper and pencil cancellation tests in which patients must cross out or circle all or a subset of items in a large array of stimuli. Specifically, participants searched for “gold nugget” rewards hidden under 48 pictures of stones that were displayed on a touch-sensitive computer monitor (Fig. 1A). The search items varied slightly in shape and colour but contained no information about reward location. Average reward probability over the search array was set at constant $p=.5$ and participants were allowed to freely sample any location, in any order and at their own pace until they had touched 20 stones. This procedure was repeated seven times in a single session. The first and last runs used a spatially uniform reward probability distribution and served as initial and final reference conditions. Critically, the reward probability distributions were manipulated during the five intermediate runs using an online adaptive method. These distributions were computed so as to minimize reward probability at the most visited locations during the preceding run and maximize it at the least visited locations. This was done by

1 computing the logistic regression fit on the horizontal spatial distribution of selected items,
2 reversing the sign of its slope and normalizing it in order to obtain a new reward probability
3 distribution, but with the same average $p=.5$, for the next run.
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5 Thanks to this procedure, we aimed to estimate the extent to which spatial exploration by
6 neglect patients and a matched normal control group implicitly followed the underlying reward
7 distribution. Patients were expected to show an initial rightward tendency and therefore to be
8 presented with a subsequent left-biased reward distribution (Fig. 1B). We predicted that low reward
9 rates on the right side would induce a displacement of their spatial exploration toward the left side.
10 Note that if the observed behavior matched this prediction and patients preferentially sampled the
11 most rewarded region, they would be expected to experience both leftward and rightward shifts in
12 the reward distribution over successive runs. Although at the group level control subjects were not
13 expected to present a rightward bias, we predicted that individual subjects would not sample the
14 display in a strictly homogeneous manner, some exploring more the left side and others more the
15 right side. This would cause them to experience biased reward distributions during the intermediate
16 runs with multiple reversals of the reward distribution in subjects closely tracking its centre of
17 mass.
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31 **2. MATERIALS AND METHODS**

32 We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria,
33 whether inclusion/ exclusion criteria were established prior to data analysis, all manipulations, and
34 all measures in the study.
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40 **2.1 Participants**

41 The study was approved by the local ethics committees in Paris, Lyon and Turin and written
42 consent was obtained from all subjects in accordance with the Declaration of Helsinki. Patients
43 were recruited from the Salpêtrière Hospital (Paris, France) and from the Don Gnocchi and San
44 Camillo Hospitals (Torino, Italy). Fifteen patients with visuospatial neglect (mean age = 63.2 years;
45 education = 5.5 years) were included in the study (see Table 1). Neglect was diagnosed if apparent
46 on at least one out of three tests commonly used for neglect assessment (see below). A patient was
47 diagnosed with neglect if the bisection error exceeded a cut-off value set at two standard deviations
48 above the mean error of control subjects (Bisiach *et al.*, 1998), and/or scored
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one or higher (on a 0-3 points severity scale) on the Daisies copying task (Marshall and Halligan, 1993), and/or the difference between left sided and right sided omissions on the Diller's cancellation task (Diller and Weinberg, 1977) was ≥ 1 . All patients had brain lesions located in the right cerebral hemisphere. In some cases, the lesions extended into the subcortical space and could include basal ganglia structures. Using available documentation (CT or MRI scans and neuroradiology reports) the brain lesions were drawn on the MNI152_T1_1mm template (from FSL) in order to localize the damaged structures and estimate lesion volume (see Figure S1 for lesion reconstruction). A sample of sixteen age-matched healthy individuals with no history of brain damage was included in the study as a control group (mean age = 62.8 years; education = 9.7 years). All participants were right-handed. All were tested during a single, approximately 40 minutes-long, session. The data from all selected participants were included in the presented analyses. No part of the procedures and planned analysis described for this study were pre-registered prior to the research being conducted. The conditions of our ethics approval do not permit public archiving of anonymized study data due to risks of breaches to participant confidentiality. **The conditions of our ethics approval do not permit public archiving of anonymized study data due to risks of breaches to participant confidentiality. Access to these materials can be requested from the lead author (Jean-René Duhamel) at the Centre National de la Recherche Scientifique, and will be subjected to a formal data sharing agreement in accordance with ethical procedures governing the reuse of clinical data. Task presentation and analysis codes are publicly available at <https://osf.io/rx3av/>.**

Table 1.

Patient ID	Sex	Age	Time post lesion (days)	Schol.	Bisection error		Daisies copy		Diller		Cause of stroke	Lesion
					Pre	Post	Pre	Post	Pre	Post		
CA	M	51	80	5	4,8	9,8	2	1	1	2	I	F,T,P
CH ^a	M	60	63	5	-2,8	8	3	n.a.	2	2	I	Th,IC
FE	F	67	90	5	-2,8	2	0	0	1	0	H	T,Ins
FL	M	60	82	5	12,7	8,3	1	1	0	n.a.	H	P
HE	M	65	96	5	7,7	5	n.a.	n.a.	0	0	I	T,P
MO	F	69	720	6	42	n.a.	3	n.a.	20	n.a.	I	T,P
LE	M	74	139	5	7,4	5,2	0	0	-9	-1	I	F,T,P
MA	M	60	90	6	5,6	5,6	1	1	0	0	H	F,P,IC
MT	F	71	48	5	5	3,2	2	2	0	2	I	T,P
RA	M	58	700	6	53	11,8	3	3	9	2	H	F,T,P,CC

RO	M	71	120	5	6	5,6	3	0	3	1	H	F
AG ^b	M	62	150	5	7,8	9,6	3	3	6	12	I	Th,BG
FR ^b	F	67	46	2	8,3	n.a.	2	3	0	0	I	IC,BG
GR ^b	F	50	260	13	35	3	2	2	0	2	H	F,T,P,BG
TA ^b	M	63	90	5	-5,5	-4,5	1	0	0	0	I	F,T,P,BG

^aPatient CH had a mostly subcortical lesion and clinical picture of neglect but no evidence of basal ganglia damage, was included in the main group of neglect patients.

^bPatients with basal ganglia damage.

Line Bisection: positive values indicate a rightward bisection error in mm. Italic values indicates error >1 s.d. from normative group (Bisiach *et al.*, 1998), bold values errors > 2 s.d.

Daisies copy: neglect severity on a 4 points scale: 0 = no left sided omissions, 1 = 1/2 left sided omissions, 2 = 3 /4 left sided omissions, 3 = 5 or more left sided omissions). Values in bold are indicative of the presence of neglect.

Diller letter cancellation: score is the difference between left- and right-side omitted targets. Values in bold are indicative of the presence of neglect.

n.a.= datum not available.

Cause of Stroke: I= Ischemic; H= Hemorrhagic; Lesion: BG=basal ganglia, CC= corpus callosum, F=frontal lobe , IC= internal capsule, Ins= Insula, LN=lenticular nucleus, P=parietal lobe, SeC= semioval center, T=temporal lobe, Th= thalamus.

2.2 Virtual foraging game

The main experimental task was framed as a foraging game, nicknamed Klondike, in which subjects searched for gold nuggets hidden under stones. The participant was seated in front of a touch-sensitive 17" LCD display (ELO 1715L) placed at a distance of approximately 50 cm on which appeared a grid of 48 (8 columns x 6 rows) pictures of stones slightly different in shape, orientation and colour nuances (see Fig. 1A). A fixed overall number of gold nuggets were "hidden" under the stones and the subject's task was to uncover as many nuggets as possible by touching the stone pictures with the right index finger, with no limit of time. The visual aspect of the stones was not informative as to the presence or absence of a hidden gold nugget, which depended only on a reward probability distribution, as explained below. During a single test run, the subject sampled 20 different stone locations. Each time a stone was touched, an outcome was drawn by the computer according to a predetermined probability and the stone image was replaced for 1 sec. by a picture of either a gold nugget (in case of reward), a red scorpion image (in case of no reward) or a red "!" character (in case the same location had been previously sampled), followed by the return of the stone picture. Repeated touches on the same stone did not trigger further draws. Not leaving previously sampled stones uncovered allowed estimation of the subjects' short-term spatial memory and perseveration tendencies. Feedback on cumulated gains/losses was provided after each touch by briefly displaying (1.5 sec.) at the centre of the screen a moneybag symbol and the cumulative virtual money amount earned (+1€ for each nugget discovered, -0.50€ for each

scorpion discovered). All patients were tested in a single session and completed seven consecutive 20-trial runs that differed only in the associated reward spatial probability distribution. **Before starting the first run, participants were explained how the task will unfold and the meaning of to the different symbols on the display.** The displays, task sequence, and data recording were programmed in Matlab (The MathWorks, Inc.).

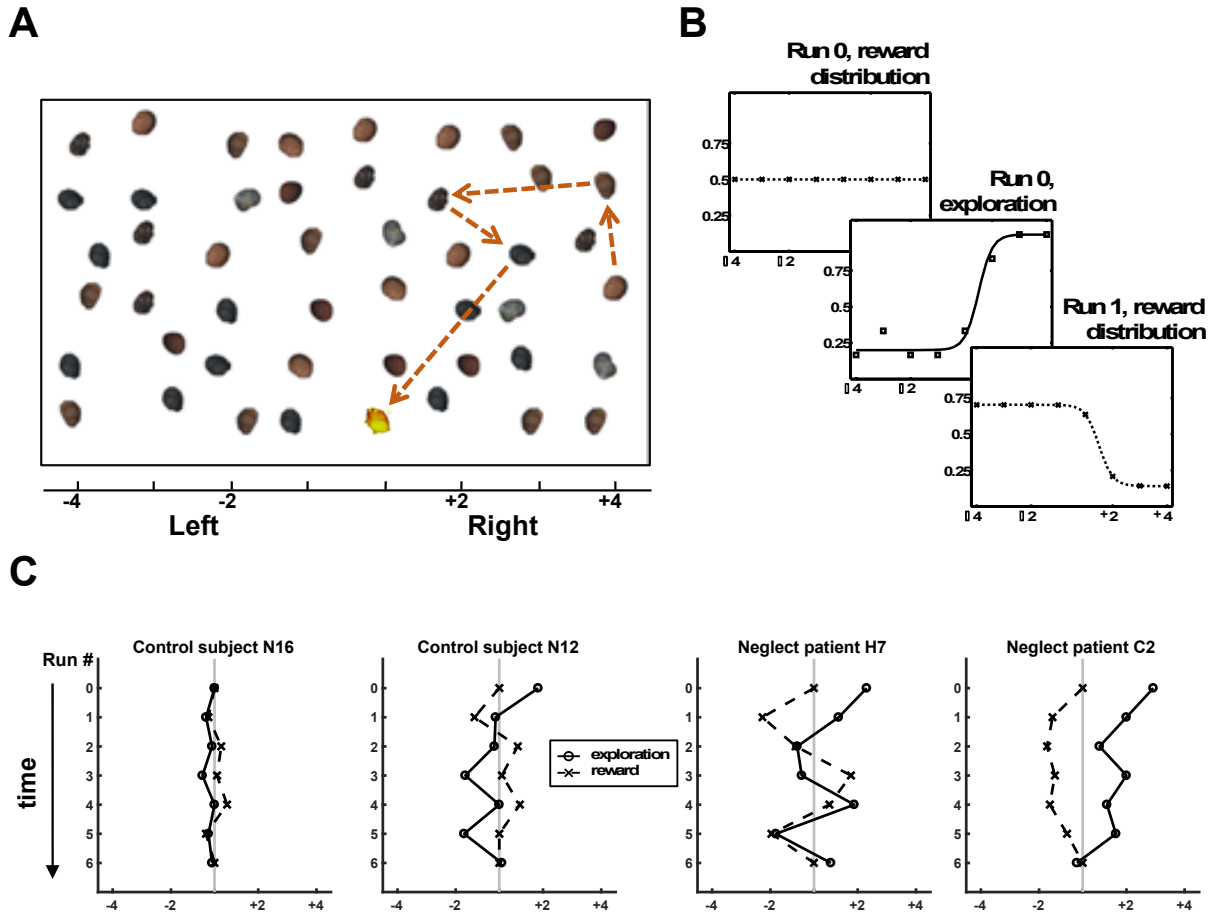


Figure 1. Foraging task and reward probability distributions. A) Stimulus array consisting of 48 stone images display on a touch-sensitive monitor and a hypothetical exploration path leading to the discovery of a gold nugget earning the participant virtual 1€. B) *Upper panel*: reward probability at all locations along the horizontal axis is initially set at $p=0.5$ at run 0; *middle panel*: hypothetical distribution of stone selections by a neglect patient and logistic regression fit at run 0; *lower panel*: adjusted spatial reward probability distribution at run 1, obtained by inverting the run 0 logistic fit (see text for details) thus devaluing previously most-visited locations and revaluating previously least-visited locations. C) Actual data from four representative control and neglect participants showing the barycenter of spatial exploration from run 0 to run 6 and its relation to reward probability distribution barycenter (see Fig. S2 for further examples).

2.3 Reward spatial probability distribution

During the initial (pre-training, Run 0) and final runs (post-training, Run 6), the reward distribution was spatially uniform and set to $p=0.5$ at each target location (see Fig. 1B). These pre- and post-

training runs served to establish the degree of rightward exploration bias in neglect patients before and after the game, respectively. For the intermediate test runs (1-5), the reward distribution was computed online for each subject according to his/her spatial exploration pattern on the immediately preceding run, such that the most frequently explored locations were assigned the lowest reward probability and the least explored ones the highest reward probability. We manipulated the reward distribution along the horizontal dimension exclusively. Formally the reward probability distribution applied in run R_{n+1} was computed by fitting the number of stone touches in each of the eight columns of the display grid during run R_n with a logistic regression function of the general form: $P=b_0/(1+\exp[-b_1-b_2*H])$, where P is the touch probability, H the stone horizontal location, b_0 , b_1 and b_2 the fitted parameters (Fig. 1B, middle panel). The sign of the slope was then inverted and the function normalized to maintain a mean reward probability over the entire workspace at a constant $p=0.5$. This new function was used to compute the reward probabilities at each horizontal stone location (Fig. 1B, bottom panel). For example, a patient with neglect who exhibited a strong rightward exploration bias on run R_0 , would be assigned on run R_1 a reward distribution with a very low probability on the rightmost portion of the workspace and conversely very high probability anywhere to the left of the prior exploration focus (see Fig. 1B). Reward distributions were dynamically adjusted in this way before the start of each new run in order to steer the subject away from the regions of the workspace that were most explored on the previous run (see Fig. 1C). This procedure could therefore lead a subject who showed an initial exploration bias but who closely tracked the reward distribution, to experience multiple reversals of the reward spatial probability distribution over the course of the experiment. We expected this to occur most often in control subjects but also in neglect patients, depending on the severity of the exploration bias and the degree of sensitivity to reward effects.

2.4 Clinical assessment of neglect

Standard line bisection (Schenkenberg *et al.*, 1980), copying (Marshall and Halligan, 1993) and a computer-based version of the Diller's letter H cancellation (Diller and Weinberg, 1977) tests were administered to neglect patients before and after completing the experimental task in order to assess the presence of neglect and possible generalization of training. Cut off score on line bisection was based on previously collected normative data from a group of 40 normal controls matched with neglect patients for age and educational level (Bisiach *et al.*, 1998). Line bisection. Patients were required to bisect at the middle, by means of a pencil, a series of five 180 mm long and 1 mm thick black horizontal lines presented, in turn, on a table desk and printed centrally along the major axis of an A4 sheet of white paper, whose minor axis lay on the anterior extension of their trunk's

midsagittal plane. Errors were measured with approximation to the nearest mm. For each patient, record was taken of the mean bisection error. Daisies copying. Patients were asked to copy the picture of a flower pot, composed of two branches of daisies. The image is symmetrical along the left-right axis. Omission of the left flower as a whole or of a number of details are indicative of the presence of egocentric neglect (Marshall and Halligan, 1993). The experimenter scanned each copy from left to right in search of omissions: depending on the number of omitted details, each copied half daisy was attributed a neglect severity score on a 4-point scale (0 = no omissions, 1 = 1-2 omissions, 2 = 3 – 4 omissions, 3 = 5 or more omissions); the left-to-right sum of the scores attributed to each half daisy was held to represent the severity of neglect (Pia *et al.*, 2004). Computerized Diller's task. Patients were presented with 48 capital H letters appearing on a touch-sensitive 17" LCD computer monitor. They had to cancel out all letters by touching each one with their right index finger, with no time limitation and we computed the difference between left- and right-sided omissions. In order to obtain a global indicator of neglect, we also computed a comprehensive Neglect Severity Score (NSS) by converting the patients' scores on each of the three tests into a z-score or pseudo z-score (capped to 3) and combining these linearly. For line bisection, z-score conversion was obtained directly from normative data (Bisiach *et al.*, 1998). For daisies copying, we used the raw scores, which are already in the 0-3 targeted range. For letter cancellation, we defined boundaries for number of omissions as follows: $<1 = 0$, $1:2 = 1$, $3:8 = 2$, $>8 = 3$. The resulting three scores were attributed the same weight and summated, yielding individual NSS values between 0 and 9. On the few instances where results were not available in one of the tests, it was replaced by the mean value of the other z-scores.

2.5 Statistical analysis

All statistical analyses were performed using Matlab (The MathWorks, Inc.) built-in Statistical Toolbox. Analyses were conducted on the spatial distribution of screen touches by computing the barycenter (weighted average location) of touched items in the horizontal dimension. Comparison between the performance of patient and control participants and between initial and final runs of the task were carried out using repeated-measures ANOVA and multiple comparisons (Tukey-Kramer method). A similar analysis was conducted on two other dependent variables: number of repeated touches at the same location and response latency. We also examined dependencies between changes in spatial exploration and in reward distribution barycenters over successive runs using linear regression analysis. Horizontal barycenters were obtained by computing the weighted average location among the 8 possible column positions. Finally, we quantified, for each participant, the impact of winning and losing streaks on foraging strategy by computing travel

distance (Euclidian distance between starting and ending position expressed in percentage of screen size) and angle (angular difference between previous and current displacement vectors) after each sequence of two or more reward discoveries and each sequence of two or more reward non-discoveries. Differences between the effect of winning and losing on these two parameters were assessed using Student's t-tests. All statistical tests were two-tailed.

3. RESULTS

3.1 Spatial exploration under biased reward distributions.

We used as main estimate of spatial exploration bias the barycenter of all sampled locations. The same estimate was used to characterize the underlying reward distribution. Examination of how individual subjects' performance evolved from the first to the last test runs (Fig. 1C and Fig. S2A) reveals a distinct parallelism between the displacement of the exploration barycenter (EB) and of the reward distribution barycenter (RB). Even when there is a spatial offset between EB and RB, indicating that the subject did not quite find the reward "hot spot", spatial exploration appears to shift in conjunction with the reward distribution (e.g. control subject N12 in Fig. 1C). The two patients illustrated in Fig. 1C also show this reward tracking pattern as well as progressive improvement of their neglect, a point that will be discussed below. In order to quantify this modulation of spatial exploration by reward, we examined the correlation between changes in EB and in RB across successive runs.

As shown in Fig. 2, RB shifts predict EB shifts in both controls subjects ($r=0.66$, $p<.0001$, linear regression, $R^2=0.43$, $F(1,73)=54.56$, $p<.0001$) and neglect patients ($r=0.42$, $p<.001$, linear regression $R^2=0.18$, $F(1,73)=16.13$ $p<.001$; see also Fig. S3 showing for the same correlation data, individual subjects regressions confirming that reward tracking is a common feature that does not merely emerge as a result of averaging across individuals). Reward distributions shifts were not imposed *a priori*, but were empirically determined in order to counteract subjects' exploration bias on the preceding test run. Thus neglect patients, like control subjects, could experience both negative (leftward) and positive (rightward) RB shifts: although an initial right-sided bias would condition the introduction of a left-biased distribution, sufficient left neglect compensation could call for an inversion of the reward distribution favouring exploration of the right side of space on the next run (e.g. patient H7 in Fig. 1C; see Fig S2B for the complete set of reward probability distributions used in control and patient participants). Interestingly, this effect is not mediated by conscious processing, as post-test debriefing revealed that neither patients nor control subjects became aware of reward distribution changes from one run to the next. When probed about their

strategy, some participants reported that they used hue or shape cues in the stone images to guide their search, but none indicated that they felt that rewards were more concentrated in some regions than others. To sum up, these results indicate that the spatial exploration behavior of patients with neglect, similarly to that of controls, is covertly influenced by the spatial distribution of the rewards, leading them to explore the side of space where the probability of being rewarded is higher, irrespective of whether it is in the neglected or in the non-neglected portion of space.

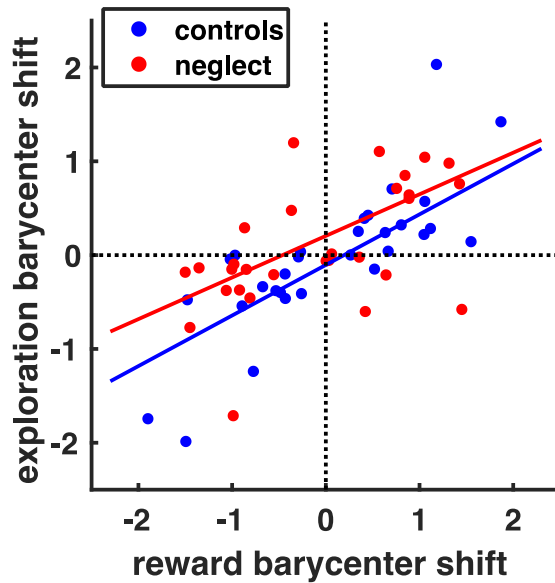
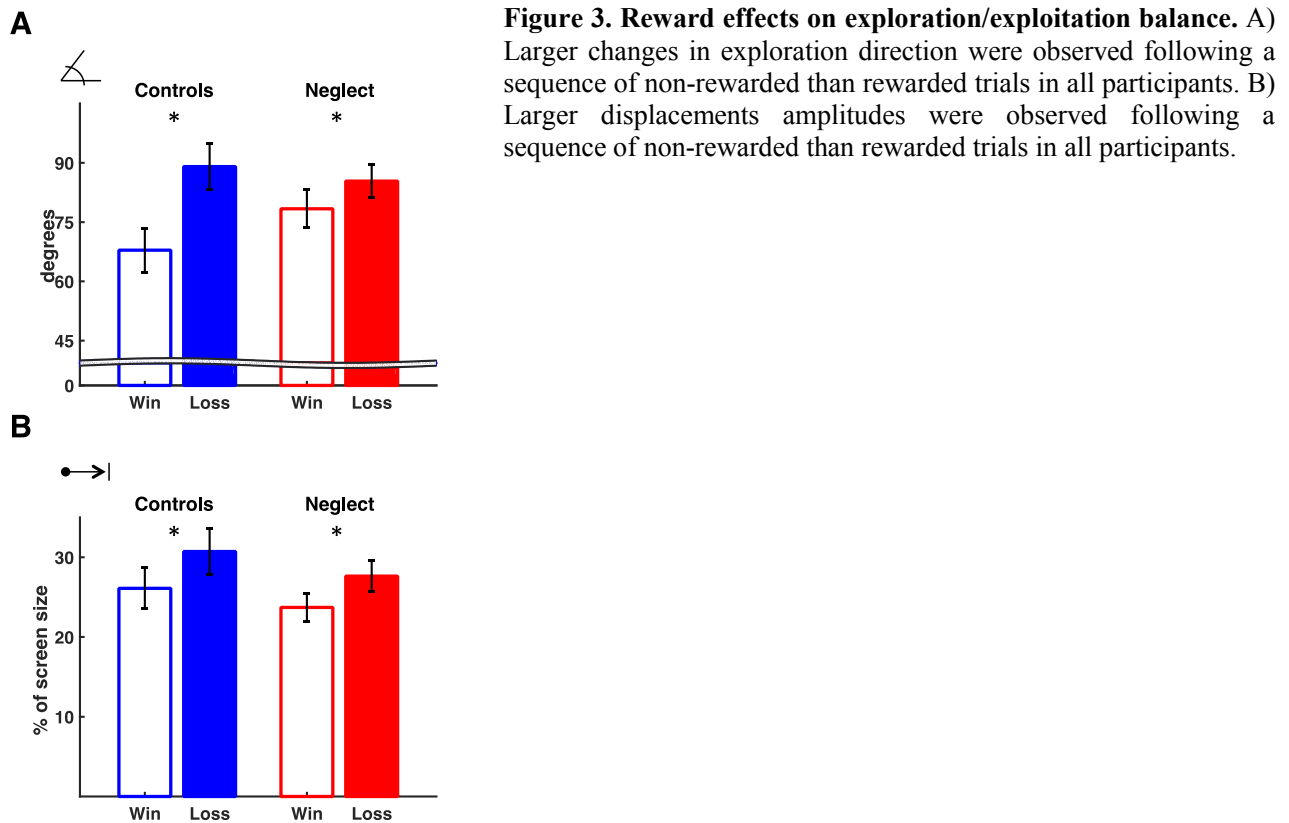


Figure 2. Correlation between exploration and reward barycenter. Spatial exploration shifts in conjunction with the displacement of the reward spatial probability distribution from one run to the next in control subjects (blue dots) and in neglect patients (red dots) and fitted linear least-square regression line.

3.2 Exploration/exploitation.

Foraging behavior (Stephens and Krebs, 1986; Krebs *et al.*, 1974) involves making decisions about whether to spend time harvesting food from a progressively depleting patch or to depart and allocate that time toward seeking a fresh patch. Such stay versus switch decisions have been successfully predicted by optimal foraging theory in different contexts (Charnov, 1976). This framework offers an opportunity to assess sensitivity to immediate reward contingencies. Here, we simply assume different behaviors following winning and losing streaks and predict that a sequence of losses will cause larger changes in exploration direction and larger displacement amplitudes in order to move away from regions where rewards are scarce and seek more promising spots. In order to test this prediction, we computed two simple measures: the travel distance and the change in travel direction between the current and the next chosen stone (excluding cases where a direction change was imposed by the environment, like having just sampled a stone located on an edge of the display). For each measure, we tested the hypothesis that a larger change occurred after a losing than a winning sequence ($n \geq 2$ successive wins and losses, respectively). The results shown in Fig. 3 indicate that this was indeed the case, with significant effects for both variables in control participants (resp. $T(14)=3.54$, $p<.005$ and $T(14)=2.46$, $p<.05$ for angle and direction). The effects

were also observed in neglect participants (resp. $T(14)=3.31$, $p<.01$ and $T(14)=4.25$, $p<.001$ for angle and direction). This exploratory behavior is comparable to that displayed by a number of animal species (Bell, 1990; Weimerskirch *et al.*, 2007), as well as by humans in virtual foraging environments (Hills *et al.*, 2013), and suggests that control subjects and patients alike adapt their short range exploration strategy to proximal reward opportunities.



3.3 Changes in neglect-related behavior.

We assessed whether neglect-related behaviors changed after five consecutive runs of spatial exploration under biased reward distributions, by comparing performances on the initial and final runs, both of which involved uniformly distributed rewards. Inspection of the percentage of touches as a function of item location shows an initial marked left-right asymmetry in neglect patient as compared to control subjects (Fig. 4A, Run0 Group X Position interaction: $F(7,216)=4.47$, $p<.0001$; Tukey-Kramer post-hoc comparisons show significantly more touches on the two rightmost positions than on the four left positions in patients and no differences between any positions in controls, $p<.01$). After training, this asymmetry was reduced in neglect patients, although the leftmost items remained largely ignored (Run6 Group X Position interaction: $F(7,216)=4.82$, $p<.0001$; post-hoc comparisons show significantly fewer touches on the leftmost position than all

1 other positions in patients and no differences between any positions in controls, $p < .01$). A global
2 assessment of these effects was carried out using a repeated-measures ANOVA on the exploration
3 barycenters (Fig 4B) which showed a significant Group effect ($F(1,27)=20.31$, $p < .001$) reflecting the
4 rightward deviation of the neglect patients' touches and a significant Training ($F(1,27)=4.12$, $p < .05$)
5 effect showing a lesser exploration asymmetry after training. The Group x Training interaction
6 failed to reach significance $F(1,27)=2.9$, $p = .10$), but in consideration of the result of the analysis
7 conducted on the data shown in Fig 4A, the effect of training on exploration barycenters seems to
8 reflect neglect patients' lesser exploration of the rightmost positions and increased exploration of
9 the left positions closest to the midline.

10 Patients sampled the same item multiple times in the right hemispace (Fig. 4C). One might ask if
11 such return visits constitute perseverative responses, i.e. the compulsory repetition of the same
12 action, or a failure of spatial working memory. Close inspection of these data indicates that most
13 revisits are not immediate perseverative responses (which represent a mere 3.8% of all revisits) but
14 were made several trials after the initial visit. We found that, in addition to being more frequent,
15 neglect patients' return visits occur earlier after the initial visit than in control subjects (mean=
16 10.29 trials vs. 12.38 trials, for neglect and control subjects, respectively, $T[24] = 2.09$, $p = .0475$).
17 Return visits were equally likely at previously rewarded and unrewarded locations (neglect patients:
18 $p = .48$ vs $.52$, control subjects: $p = .51$ vs $.49$, respectively), which is somewhat expected given that in
19 the present task, only the location, and not the associated outcome, of prior visits need to be tracked
20 in order to avoid needless and ineffective returns. When they do occur, revisits are thus likely due to
21 capacity limitation and trace decay in working memory. After training, the rate of revisits
22 decreased significantly although it remained more elevated than in control subjects (Group x
23 Training interaction $F(1,27)=4.36$, $p < .05$). Taken together, these results suggest that in addition to a
24 unilateral spatial attention deficit, neglect patient present impairments in spatial working memory
25 (as suggested by e.g. Wojciulik et al., 2001) that can be improved through training.

26 Finally, decision times, defined as the interval time between two successive responses, were slower
27 in patients than control subjects but this difference decreased between the initial and final tests
28 (Group x Training interaction $F(1,27)=16.43$, $p < .001$, Fig. 4D). This effect had no spatial specificity
29 and may indicate that with repeated testing patients performed the task more efficiently, or showed
30 enhanced arousal and/or motivation. Overall, these data are indicative of a significant amelioration
31 of the left space processing following reward-based training in neglect patients.

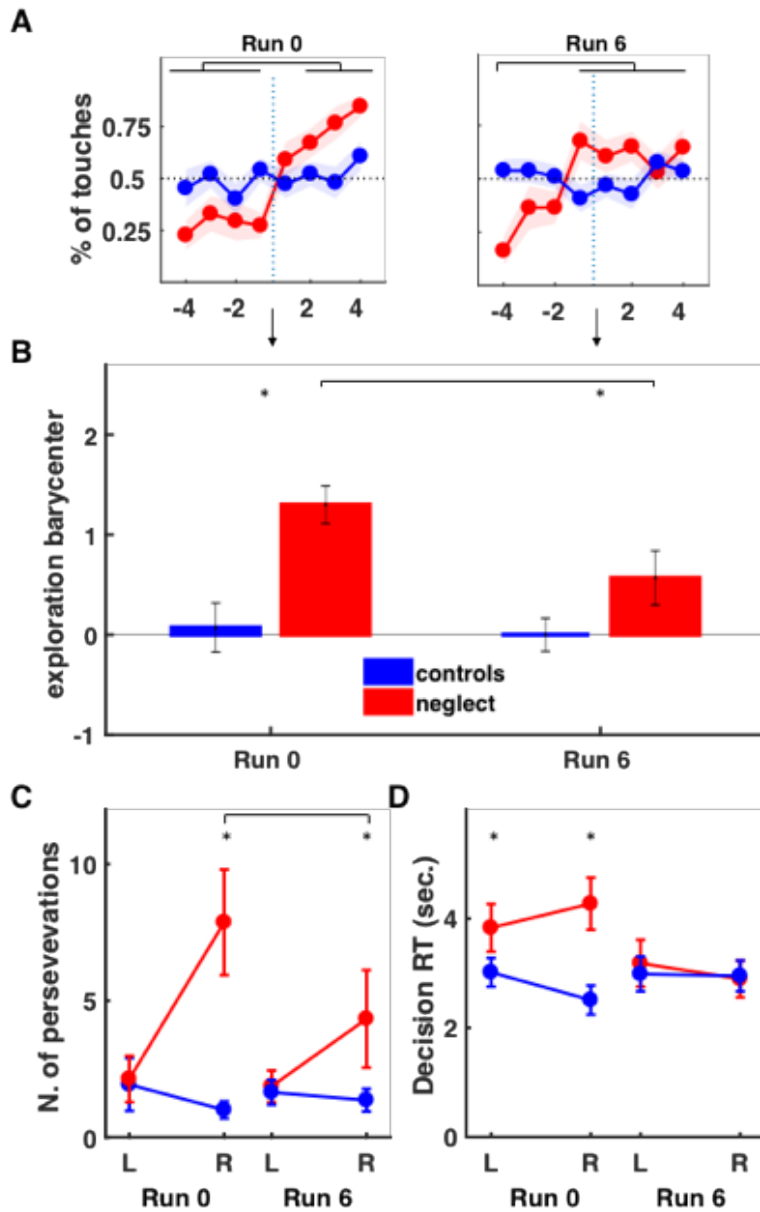


Figure 4. Changes in spatial exploration behavior after training. A) Mean percentage of selected stones as a function of item horizontal position at run 0 (left panel) and run 6 (right panel)). Shaded area illustrates SEM above and below the mean. B) Same data summarized as mean barycenter of spatial exploration, show absence of exploration bias in the control group, significant reduction of the rightward bias in neglect patients at run 6 (* indicate a significant difference between the considered value and the corresponding value in the control group). C) Mean number of perseverations, i.e. revisits of the same items, on the left and right side of the display. Perseverations were common in the right hemispace and decreased between run 0 and run 6 but remained significantly elevated as compared to control participants. D) Mean decision time, measured as time between two item selections, was slower in the patient group but decreased significantly from run 0 to run 6. Error bars in B,C,D correspond to SEM.

3.4 Predictors of spatial exploration improvement.

The observed amelioration of left space exploration in the neglect group may occult possible individual variability in training effects. In order to better understand whether reward manipulations might benefit some patients more than others, we applied multiple linear regression analysis to assess changes in spatial exploration, using clinical variables listed in Table 1 as predictors, namely

patients' age, time since lesion, bisection and Diller letter cancellation performed prior to the present study (daisies copying performance was not included as data was missing from one patient). We also used estimated lesion size and presence of basal ganglia damage as predictors (Fig. S1), in consideration of the potential role of these subcortical regions in reward-based learning (Graybiel, 1995). Change in exploration barycenter was computed as the simple ratio $[EB_{Run0} - EB_{Run6}] / [EB_{Run0} + EB_{Run6}]$. This regression model accounted for about 88% of the variance in training effects ($R^2=0.881$, $F(1,8)=9.89$, $p<.005$). Inspection of the regression coefficients highlight Time since lesion onset and Bisection test performance as key predictors and, to a lesser extent, Lesion size and Basal ganglia damage (Suppl Table 1). In short, patients who improved the most were those who were tested shortly after lesion onset (2-4 months), exhibited moderate neglect and had circumscribed lesions sparing the basal ganglia. However, caution should be taken in interpreting the result of this analysis given the small size of our patient group.

3.5 Relation to other measures of neglect.

Performance on standard paper and pencil bisection, copying and cancellation tasks served to document clinical neglect in patients. In order to determine whether the effects of spatial exploration training were context-specific or could influence neglect measured by other means, these three tests were administered to patients before and after completion of the testing session. Despite the presence of a trend, no significant changes were found on measures of line bisection, daisies copying and Diller letter cancellation. However, since neglect is a clinically heterogeneous syndrome, individual patients may exhibit presence, absence or varying degrees of impairments on the different tests. In fact, in our patient group, the three tests correlated only moderately with each other, the only statistically significant correlation being that between copying and cancellation (Bisection x Copying $R=0.47$, $p=0.10$; Bisection x Cancellation, $R=0.48$, $p=0.09$; Copying and Cancellation, $R=0.62$, $p=0.02$), and therefore probably measure partially separable aspects of the neglect syndrome. We reasoned that combining the performance measured on each of the clinical tests could yield a more robust and sensitive index of neglect severity. We therefore computed a comprehensive normalized Neglect Severity Score (NSS, see Methods) to assess changes in neglect before and after training. A modest but significant change was observed (NSS_{pre} mean= 4.00, s.d.= 2.39; NSS_{post} mean=2.82, s.d.= 1.84, $t(13)=2.5222$, $p= 0.0255$), suggesting that training could also ameliorate other neglect-related behaviors.

4. DISCUSSION

Reward is a potent modulator of behavior, which can shape object and action selection as well as orient spatial exploration (Kim and Hikosaka, 2015). The present findings show that in patients with hemispatial neglect, reward signals are processed in both the neglected and non-neglected sectors of space. Manipulating the spatial gradient of reward distributions produced systematic effects on foraging behavior, with shifts in exploration tracking shifts in reward probability. Repeated exposure to biased reward distributions over the course of a single 40-minute session, significantly modified spatial exploration in neglect patients, when comparing the initial and final runs performed under homogeneous reward distribution. This result is consistent with a previous study showing that increasing the reward value of left targets improves visual search performance in neglect patients (Lucas et al., 2013). Also consistent with this study is the fact that neither the patients nor the control subjects became aware of the reward probability distribution asymmetries that shaped their exploration behavior, indicating that this type of learning is implicit and involves no conscious mediation.

The present procedure was not *a priori* designed to systematically reinforce exploration of the left at the expense of the right hemispace, but to counteract spatial exploration asymmetries, regardless of their direction. In practice, because neglect patients over-explored the right side in the initial run, they were subsequently exposed to reward distributions designed to make left-sided locations more rewarding and right-sided locations less rewarding. This led patients to explore less the ipsilesional locations and venture more toward the left hemispace and, over successive runs, to show more balanced sampling of left and right items. However, the algorithm that computed the next run's reward distribution, did not "insist" on drawing neglect patients ever more toward the left side. That is, if their exploration barycenter was sufficiently close to the midline, the computed future reward distribution was only slightly asymmetric. Furthermore, on some of the runs, several neglect patients responded strongly enough to left-biased reward distributions that they explored the left side of space more than the right side and this resulted in the next run's reward distributions to be right-biased (e.g. case H7 in Fig. 1C and Fig. S2A). This might explain why the leftmost items on the display were still largely unexplored on the last testing run (Fig 4A), a limitation that should be taken into consideration if reward-based training were to be used for rehabilitation purposes. In fact, the adaptive procedure that we used may not have served so much to counteract neglect behavior as to promote more flexible and efficient spatial exploration in a changing environment. Although this is a worthy therapeutic objective on its own, achieving a more complete correction of neglect might require reinforcing left-hemispace exploration more consistently than was done in the present study.

1 Our training procedure promoted, over time, not only a broader sampling of the
2 environment but also better self-monitoring of actions (i.e. fewer return visits to previously
3 explored locations) and more efficient search (i.e. shorter dwell times). Motor monitoring
4 impairments characterized by perseverative motor responses in the ipsilesional hemispace are not
5 uncommon in neglect patients, notably in the presence of frontal lesions (Pia *et al.*, 2009; Pia *et al.*,
6 2013; Rusconi *et al.*, 2002). This has been interpreted as a consequence of motor disinhibition
7 (Vallar *et al.*, 2006) and/or spatial working memory deficits (Wojciulik *et al.*, 2001). In the present
8 study, neglect patients' number of repetitive touches on right-sided items was initially significantly
9 higher than on left-sided items. Interestingly, at the end of the training procedure, the number of
10 right-sided perseverations had decreased significantly. This suggest that the negative reward
11 contingencies associated with the right hemispace helped restore the inhibitory control normally
12 exerted by the frontal lobe (see Aron *et al.*, 2004 for a review) and its ability to detect errors in
13 motor performance (Gemba *et al.*, 1986). It is also possible that value signals (both positive and
14 negative) enhance spatial working memory, by reinforcing the trace of previously visited locations,
15 thus preventing needless revisits. Such effects are consistent with the observed modulations of
16 neuronal activity by stimulus value in medial prefrontal and anterior cingulate areas (Serences,
17 2008), which are known to play a role in performance monitoring (Gemba *et al.*, 1986).

18 All neglect patients were significantly quicker in deciding their next move on the last test
19 run, as compared to the first run. This might be due to a practice effect, although other factors
20 should also be considered The effect of training on decision time could be related to an amelioration
21 of attentional disengagement from the current to the next target, a mechanism previously reported to
22 be impaired in neglect (Posner *et al.*, 1984). As this change was not selective to a given region of
23 space, a general effect of heightened arousal and motivation might have contributed to improving
24 search efficiency in addition to, or independently from, spatially-specific effects of training on
25 search direction. Enhanced arousal in a reward context is plausible since it has been reported that
26 subliminal processing of reward cues is associated with increased skin conductance responses,
27 generally considered to reflect increased basal forebrain dopaminergic and noradrenergic activation
28 (Pessiglione *et al.*, 2007, Olgiati *et al.*, 2016).

29 Our study unveils some general properties of reward effects on spatial behavior. Succeeding
30 and failing to uncover a reward at a sampled location modified subjects' exploration strategy in a
31 predictable way. A series of losing, as compared to winning trials, is associated with a larger change
32 in movement direction and longer travel distance on the next trial. This result can be loosely
33 interpreted within the framework of foraging models, which relate resources-seeking behavior to
34 the so-called marginal value of foraging (Stephens and Krebs, 1986; Krebs *et al.*, 1974): as long as

the average reward rate remains high, an individual should remain in the same region, but when it falls below an estimated opportunity cost (e.g. the time and effort *not* spent harvesting a different and potentially more plentiful region), the individual is better advised to move away from the depleting region. As with other forms of trial-and-error reinforcement learning, stay or switch decisions require keeping track of recent reward history, a process believed to be mediated by midbrain dopamine signaling (Sutton and Barto, 1998). Control subjects and neglect patients show typical exploration/exploitation balance for short (2-3) trial sequences, suggesting that the mechanisms responsible for steering behavior over a brief interval and short distance depend on brain structures that are preserved in neglect patients. This is also consistent with, and could explain that the underlying reward distribution can steer patients' exploration from one run to the next as revealed by the correlations between shifts in exploration and in reward distribution barycenter. However, fostering progressive and more extensive exploration of left space in the time scale of multiple runs, likely depends from other cortical and subcortical mechanism where reward information is integrated with motor and attentional signals. In fact, previous work has shown that brain regions like orbitofrontal, medial prefrontal and anterior cingulate cortex encode search value and cost during a foraging-type task (Kolling *et al.*, 2012) and single neurons in the non-human primate ACC can hold traces of past rewards across multiple trials (Bernacchia *et al.*, 2011). We found that the rightward bias under homogenous reward distribution decreased significantly, on average, between the first and last experimental run. However, patients still systematically neglected the leftmost items and not all patients exhibited this improvement. Multiple regression showed that different variables were associated with the training's impact or lack thereof. Patients with marked clinical neglect showed less change in exploration, suggesting that reward effects may not be strong enough to overcome core visuo-spatial attention deficits. A window of plasticity may also exist for reward-based training as patients tested long after their cerebral injury also showed less improvement. Finally lesion size and presence of basal ganglia lesions, may also play a significant role. Although these findings should be interpreted cautiously given the small number of patients and the exploratory nature of this post-hoc analysis, they are consistent with studies in animals (Christakou *et al.*, 2005) and humans (Li *et al.*, 2018) that highlight the importance of striatal reward mechanisms in neglect and with studies that manipulated the motivational value of left *versus* right stimuli and found that subsets of neglect patients who showed little or no learning had lesions involving the right anterior cingulate region (Lecce *et al.*, 2015) or the medio-ventral prefrontal regions and extending subcortically into the basal ganglia (Lucas *et al.*, 2013). Here, we highlight a possible distinction in reward learning between short and long timescales and propose that the integrity of dopaminergic inputs to limbic, striatal prefrontal regions may be necessary in

1 order for reward-based learning to guide foraging decisions and overcome neglect patients' default
2 course of action, i.e. exploring the right hemispace.

3 Understanding the causes of, and alleviating the spatial awareness deficits of patients with
4 neglect have been major aims of research on this syndrome since its first description at the
5 beginning of the 20th century by Head and Holmes (Head and Holmes, 1911). Despite the
6 concomitant presence of anosognosia, neglect patients may transitorily overcome their spatial
7 deficit and improve their awareness of the left side of space through different interventions, such as
8 the use of prismatic goggles, stimulus saliency modulation, perceptual and semantic priming,
9 sensory and vestibular stimulation, as well as brain stimulation techniques such as transcranial
10 magnetic or direct current stimulation (for a reviews see (Luauté *et al.*, 2006)). Another potential
11 therapeutic avenue has recently been explored through the use of reward-based approaches
12 (Malhotra *et al.*, 2013; Lucas *et al.*, 2013; Lecce *et al.*, 2015). The current study sheds new light on
13 the role of reward-related stimulus salience in shaping spatial exploration and action monitoring
14 both in normal subjects and in brain damaged patients with spatial awareness deficits. Furthermore,
15 despite the only modest generalization of neglect amelioration following training - which could be
16 related to some specific features of our online adaptive procedure and to the short training duration
17 - our data suggest that reward-based training could be potentially effective in rehabilitating patients
18 with spatial and/or motor awareness deficits, via non-conscious processing of stimulus valence
19 mediated by spared subcortical reward-related neuronal networks. This field of study remains
20 largely underexplored at present and future research should aim at assessing the efficacy of such
21 reinforcement-based rehabilitative training procedures in controlled studies on right-brain damaged
22 patients with and without neglect and possibly for other categories of patients with negative
23 motivational dysfunctions, such as depressive and schizoaffective disorders.
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FUNDING

This research was funded by CNRS, University of Lyon, ANR and by LABEX CORTEX (ANR-11-LABX- 0042) grant to AS and JRD within the program “Investissements d’Avenir” (ANR-11-IDEX-0007).

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Marco Neppi-Mòdona : Conceptualization; Investigation, Data curation, Writing - original draft, Writing - review and editing

Roberta Sirovich : Formal analysis;

Alessandro Cicerale : Investigation, Data curation;

Nathalie Richard : Visualization

Pascale Pradat-Diehl : Resources; Investigation; Writing - review and editing

Angela Sirigu : Conceptualization; Writing - review and editing

Jean-René Duhamel : Conceptualization; Data curation; Formal analysis; Project administration; Funding acquisition; Writing - original draft, Writing - review and editing

Table 1.

Patient ID	Sex	Age	Time post lesion (days)	Schol.	Bisection error		Daisies copy		Diller		Cause of stroke	Lesion
					<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>		
CA	M	51	80	5	4,8	9,8	2	1	1	2	I	F,T,P
CH ^a	M	60	63	5	-2,8	8	3	n.a.	2	2	I	Th,IC
FE	F	67	90	5	-2,8	2	0	0	1	0	H	T,Ins
FL	M	60	82	5	12,7	8,3	1	1	0	n.a.	H	P
HE	M	65	96	5	7,7	5	n.a.	n.a.	0	0	I	T,P
MO	F	69	720	6	42	n.a.	3	n.a.	20	n.a.	I	T,P
LE	M	74	139	5	7,4	5,2	0	0	-9	-1	I	F,T,P
MA	M	60	90	6	5,6	5,6	1	1	0	0	H	F,P,IC
MT	F	71	48	5	5	3,2	2	2	0	2	I	T,P
RA	M	58	700	6	53	11,8	3	3	9	2	H	F,T,P,CC
RO	M	71	120	5	6	5,6	3	0	3	1	H	F
AG ^b	M	62	150	5	7,8	9,6	3	3	6	12	I	Th,BG
FR ^b	F	67	46	2	8,3	n.a.	2	3	0	0	I	IC,BG
GR ^b	F	50	260	13	35	3	2	2	0	2	H	F,T,P,BG
TA ^b	M	63	90	5	-5,5	-4,5	1	0	0	0	I	F,T,P,BG

^aPatient CH had a mostly subcortical lesion and clinical picture of neglect but no evidence of basal ganglia damage, was included in the main group of neglect patients.

^bPatients with basal ganglia damage.

Line Bisection: positive values indicate a rightward bisection error in mm. Italic values indicates error >1 s.d. from normative group (Bisiach *et al.*, 1998), bold values errors > 2 s.d.

Daisies copy: neglect severity on a 4 points scale: 0 = no left sided omissions, 1 = 1/2 left sided omissions, 2 = 3 /4 left sided omissions, 3 = 5 or more left sided omissions). Values in bold are indicative of the presence of neglect.

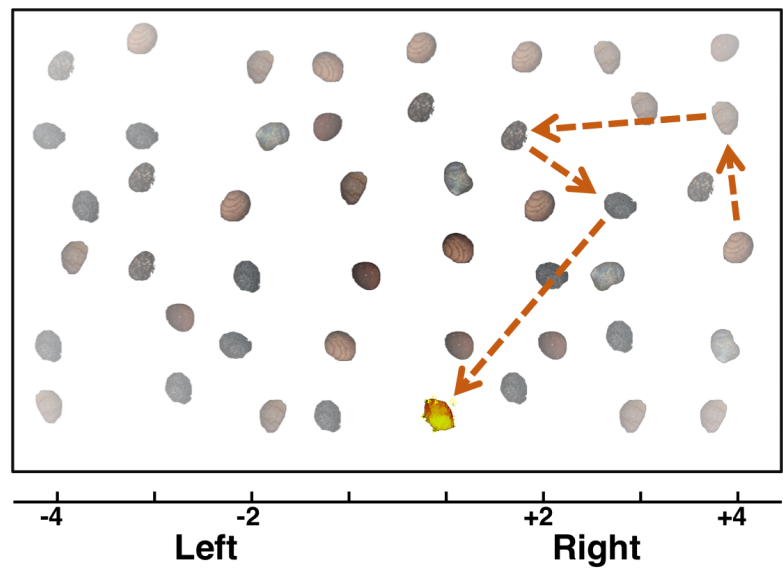
Diller letter cancellation: score is the difference between left- and right-side omitted targets. Values in bold are indicative of the presence of neglect.

n.a.= datum not available.

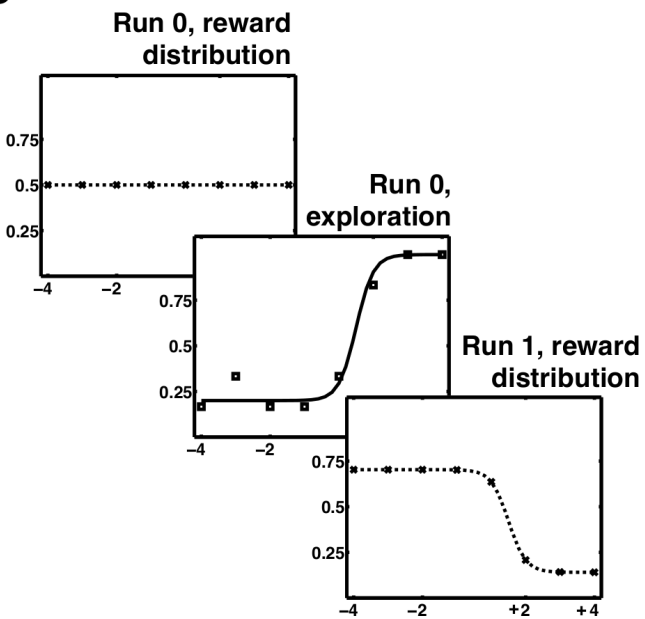
Cause of Stroke: I= Ischemic; H= Hemorrhagic; Lesion: BG=basal ganglia, CC= corpus callosum, F=frontal lobe , IC= internal capsule, Ins= Insula, LN=lenticular nucleus, P=parietal lobe, SeC= semioval center, T=temporal lobe, Th= thalamus.

Figure1

A



B



C

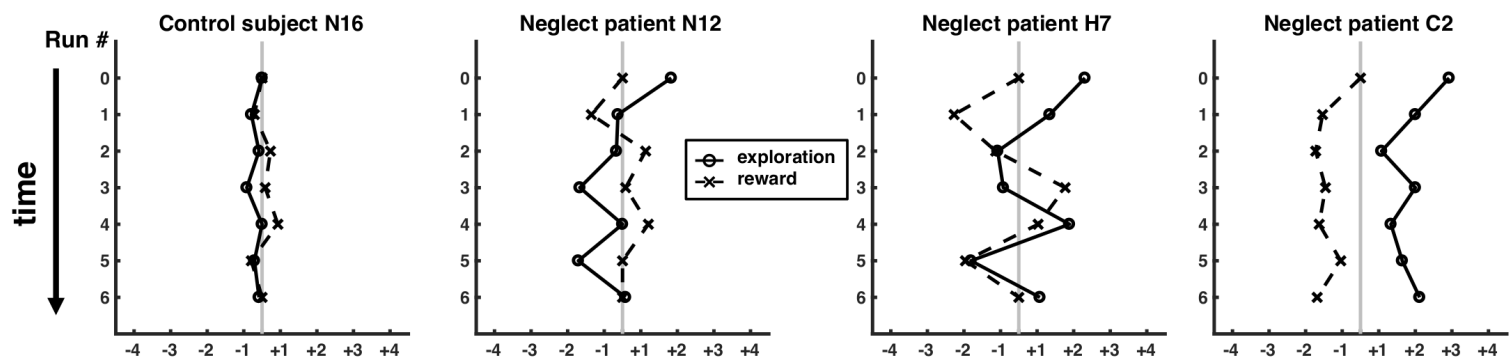


Figure2

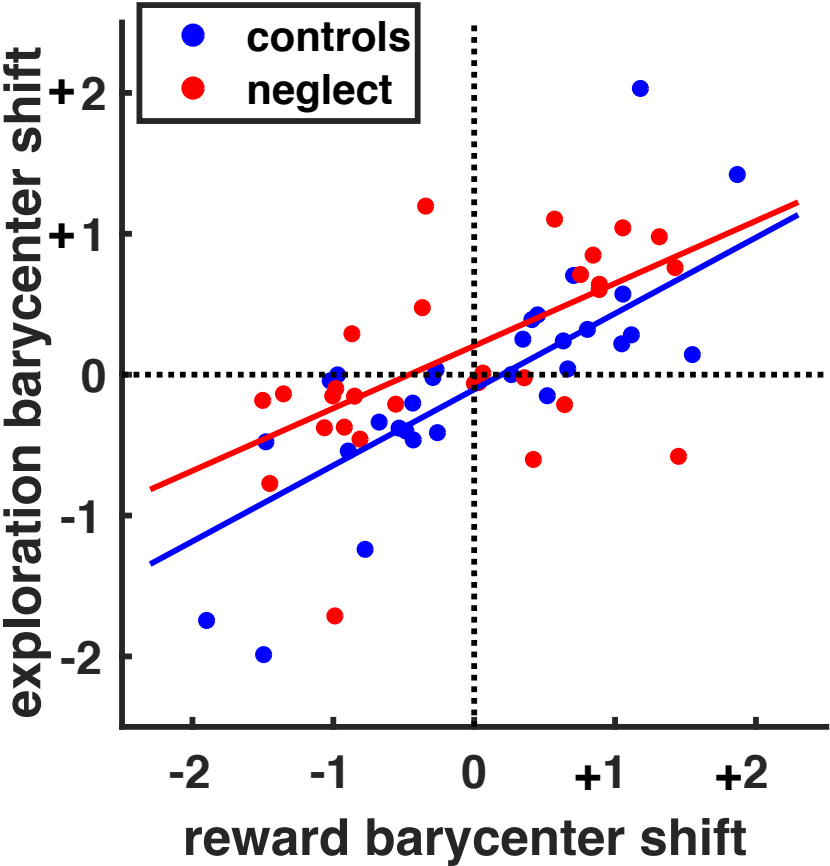


Figure3

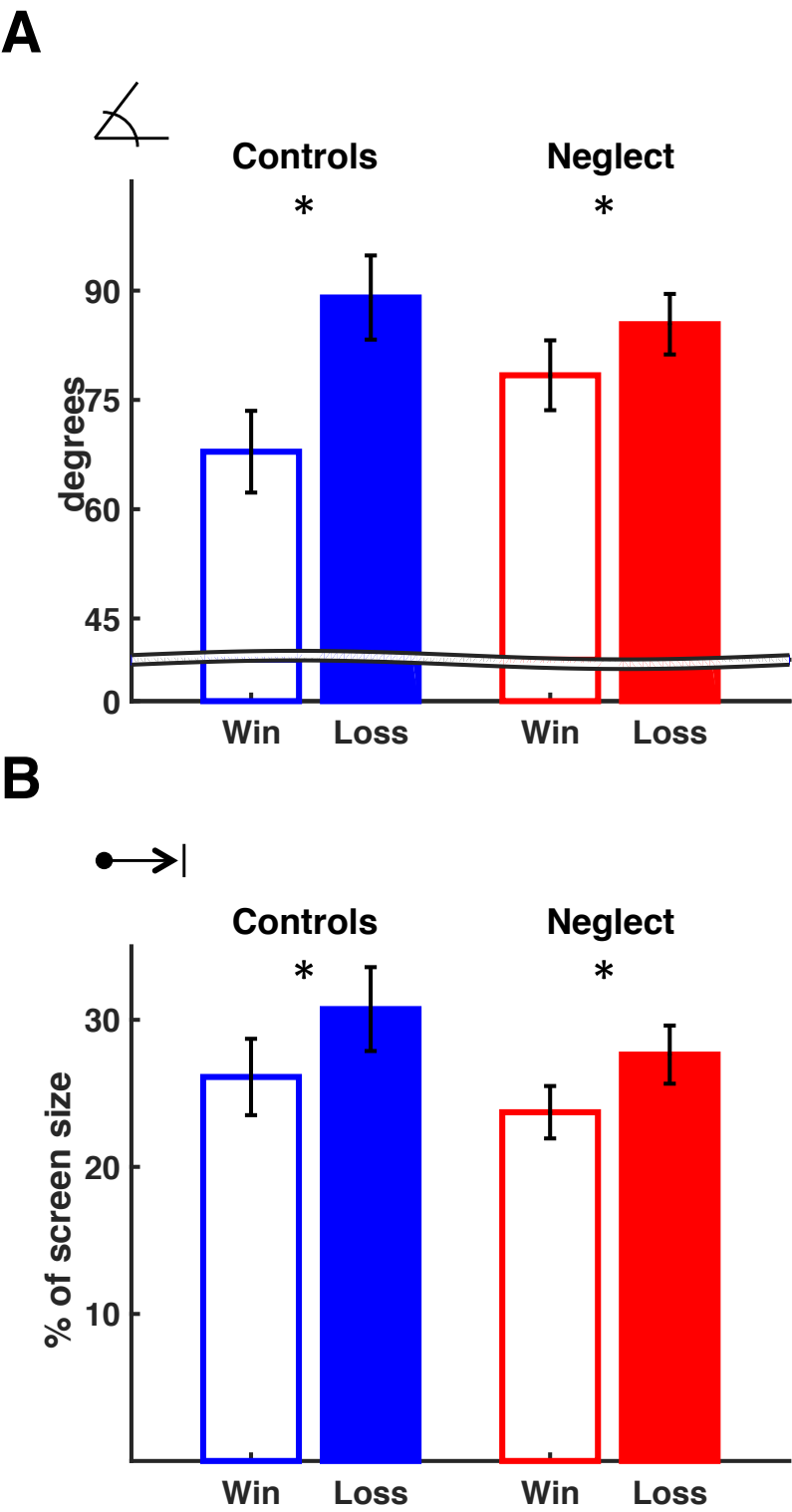
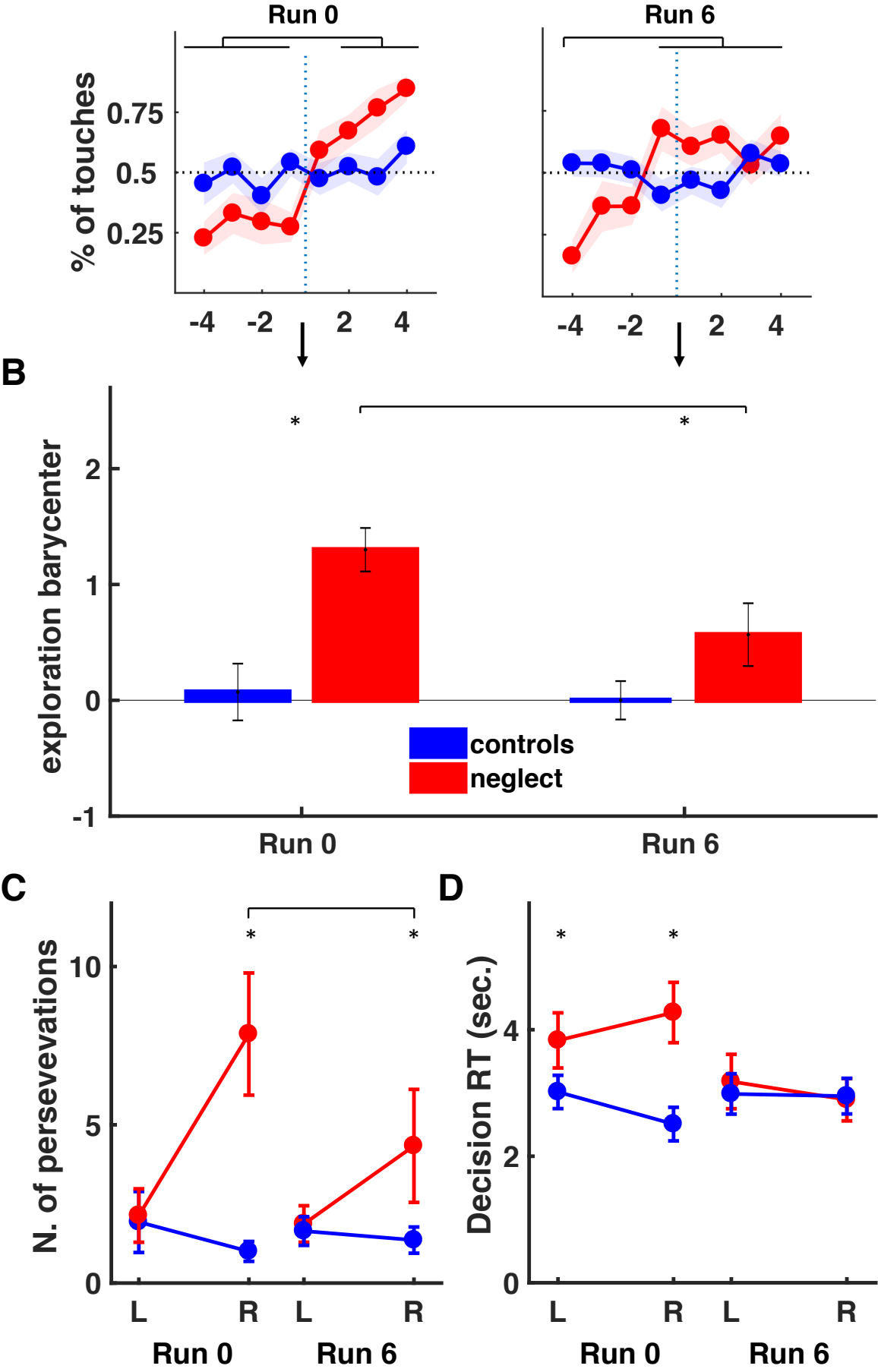


Figure 4

Figure4





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